Journal of Surgical Oncology 1999;70:217–221

Reproducibility of a Diagnosis of Invasive Lobular Carcinoma

GÁBOR CSERNI, MD*
Department of Pathology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary

Background and Objectives: The fact that invasive lobular carcinoma (ILC) is often multicentric has led to mastectomies being regularly performed for this disease in some settings. Reproducibility of the histological typing of breast cancer was investigated.
Methods: Fifty slides from breast cancers were assessed individually by 10 pathologists from different institutions, whose findings were compared.
Results: The extent of matching of the reported histological types between the various pairs of pathologists ranged between 28 and 88%. Agreement was better for pathologists with special experience in breast pathology. The kappa values for the exact histological type, for pure ILC and for the presence of an ILC component, were 0.23, 0.31, and 0.32, respectively (0.64, 0.43, and 0.46 for pathologists experienced in breast pathology).
Conclusions: The study demonstrates that there are equivocally interpreted tumors and the presence of ILC in the histological report should not serve as the sole determinant for the performance of mastectomy.
J. Surg. Oncol. 1999;70:217–221.

KEY WORDS: breast cancer; histopathological type; kappa statistics; conservative surgery

INTRODUCTION

The histological type is a factor generally recognized to influence the prognosis of breast cancers [1–3]. Current classifications differentiate several special types of invasive breast cancer, including lobular, tubular, mucinous (colloid), medullary, and some rarer variants, as well as combinations of these types; and also the remaining category of invasive "ductal" cancers of no special type (IDC NST; formerly NOS: not otherwise specified).

The reported incidence of invasive lobular carcinoma (ILC), first described by Foote and Stewart in 1946 [4], varies considerably, between 0.7 and 20% of all invasive cancers [5,6]. The classical form of this cancer features a well-described pattern of infiltration (Indian filing, and a concentric targetoid appearance around normal ducts) and a characteristic cellular composition (small, round, rather regular cells). A lack of cohesion of the cells is also rather characteristic [5,7]. Solid [8], signet-ring cell [9], tubulolobular [10], and alveolar [11] variants involving the characteristic cells but not demonstrating the typical pattern of infiltration have also been described, and a pleomorphic variant displaying the typical infiltration pattern but a more polymorphous cell population is also recognized by some [12].

The prognosis of ILC is rather controversial. Some investigators have reported a somewhat worse prognosis than for IDC [13], whereas other studies indicate a better prognosis than for IDC [14,15]. However, any prognostic advantage that there is may be due in part to the lower histological grade of these tumors [16], or may be valid for only some subtypes [2].

The incidence of bilaterality is high in all types of ILC [13,17], and multicentricity is also frequent [6,15,18]. This latter clinical association has resulted in some medical communities performing mastectomies on almost all patients with ILC. In other words, a diagnosis of ILC practically excludes breast-conserving surgery from the

Grant sponsor: János Bolyai Fellowship of the Hungarian Academy of Sciences

*Correspondence to: Dr. Gábor Cserni, Department of Pathology, Bács-Kiskun County Teaching Hospital, H-6000 Kecskemét, Nyíri út 38, Hungary. Fax No.: (36)76-481219. E-mail: cserni@freemail.c3.hu

Accepted 21 December 1998

therapeutic options in these communities, of which Hungary is an example.

In view of this clinical significance of the diagnosis of ILC, a study of the reproducibility of the histological typing of breast cancer was carried out among 10 histopathologists from different Hungarian institutions.

MATERIALS AND METHODS

Fifty slides from different breast carcinoma cases were selected from the archives of the Pathology Department of Bács-Kiskun County Teaching Hospital. The selected tumors were intended to include more ILC cases or IDC cases resembling ILC ("with lobular features") than the real-life incidence of these tumors. Some cancers of other special types were also included to serve as control cases. The 50 slides were then distributed to 10 histopathologists, working independently of one another in different institutions, with a request for histological typing.

The 10 participating histopathologists (see Acknowledgments) were all qualified and licensed to issue independent reports. Six of them had special interest and experience in breast pathology, while three others were also pathologists of great experience.

They were asked to define the type of cancer seen in the slides and to specify the types present in a case with mixed features. Cases difficult to interpret could be labeled as such. A difficulty score was later given to the so-labeled slides, indicating the number of pathologists who graded the case in question as a difficult one.

The extent of pairwise agreement was calculated for all the participating pathologists. Agreement was defined as "complete" if there were no disagreeing features, or as "combined complete or partial" if at least one component of a mixed histological type matched in both diagnoses.

Kappa statistics [19] were calculated for the overall typing of the tumors, for the reproducibility of a given histological type in this series, and for "ILC present" versus "no ILC in the lesion." Calculations were repeated after the exclusion of pathologists whose special interests and routine did not specifically include breast pathology. The following limits and labels were used to interpret agreement on the basis of kappa values: <0.00, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect [20].

RESULTS

The majority diagnoses for the individual cases, the numbers of diagnoses including ILC as a pure or mixed element of the tumor, and difficulty scores are presented in Table I. Data on the pairwise agreements are displayed in Table II. The types of diagnosis, their frequencies and the kappa values are presented in Table III. Nonsignificant values denote agreement by chance alone. Only two histological types had a better than fair reproducibility. Medullary carcinoma was in the moderately reproducible category and mucinous carcinoma was in the substantially well-reproducible one.

When the presence or absence of ILC in the diagnosis was considered (Table I), kappa was 0.32, a value significantly different from zero ($P < 0.0001$) (agreement beyond that by chance alone). This value, however, reflects suboptimal interobserver agreement.

The inclusion of only the six pathologists with special interest in breast pathology resulted in a better overall kappa value (kappa = 0.65; substantial agreement). As concerns the presence or absence of ILC in the slides, kappa was somewhat worse (kappa = 0.46; moderate agreement), but reflected a better interobserver agreement than with all 10 pathologists included.

DISCUSSION

The complete and the combined complete or partial matching of the histological types between two assessors ranged between 16 and 64%, and 28 and 88%, respectively. It was readily discerned that the third pathologist submitted the least reproducible reports on the histological types. The poor extent of the matching in general points to the need for special training courses in breast pathology for all who report on breast specimens. Excluding the third pathologist, the range of matching diagnoses was still suboptimal: 26–64% for the complete, and 30–88% for the combined complete or partial categories. The corresponding ranges for the six pathologists with special experience and interest in breast pathology were 38–64% and 58–88%, respectively.

Both the individual kappa values for the histological types and the overall kappa value reflected the suboptimal reproducibility of the histological typing in this series. Only two of the types of tumors included as controls (medullary and mucinous carcinoma) gave a better interobserver agreement. ILC was also moderately reproducible when only the six pathologists interested in breast pathology were included in the evaluation. Medullary cancer, however, was less consistently diagnosed, due to some diagnoses of atypical medullary cancers.

The lesions represented in this series included some difficult cases: 19 lesions were labeled as difficult to interpret by at least one assessor. Although all cases almost certainly involved a malignant tumor, there were four instances (0.8%) when lesions were misdiagnosed as benign. These were noted in association with ILC on three occasions and with IDC in one case, with a few cells in a fibrotic stroma: a well-recognized differential diagnostic problem. Four slides were criticized as being of poor quality, but they were rather consistently diagnosed, and accordingly they were not excluded from the analysis. On the whole, from the differences of this study and the real-life diagnostic work-up of a tumor, it can be inferred that the reproducibility of histological typing is

TABLE I. Majority Diagnoses for Individual Cases: ILC as a Component in the Tumor, and Difficulty Scores When Different From Zero

#	Majority diagnoses (No. reporting it)	ILC component in diagnosis	Difficulty scores	#	Majority diagnoses (No. reporting it)	ILC component in diagnosis	Difficulty scores
1	ILC (10)	10		26	IDC (3) or ILC + TUB (3)	6	
2	ILC (9)	9		27	IDC (5)	5	2
3	ILC (9)	10		28	ILC (9)	9	
4	ILC (4)	8	1	29	IDC (5)	5	1
5	ILC (4)	6	1	30	IDC (8)	2	
6	ILC (6)	6		31	ILC (4) or IDC (4)	6	2
7	MUC (9)	1		32	ILC (10)	10	
8	IDC (5)	3	3	33	ILC + IDC (6)	7	2
9	ILC (7)	7	1	34	IDC (6)	4	2
10	ILC (7)	8		35	MED (7)	0	
11	IDC (5)	0		36	IDC (4)	1	
12	ILC (7)	8		37	ILC (5)	6	
13	ILC (5)	8		38	IDC (6)	4	
14	MED (6)	0	1	39	IDC (4)	5	
15	IDC (9)	0		40	IDC (4)	5	
16	IDC (5)	4	5	41	ILC + IDC (3)	8	1
17	IDC (7)	3	2	42	IDC (5)	0	
18	IDC (4)	1		43	IDC (6)	3	
19	IDC (8)	1	1	44	IDC (4)	3	
20	IDC (8)	2		45	IDC (5)	5	1
21	ILC (5)	6		46	ILC (5)	9	
22	IDC (7)	3	3	47	MED (7)	0	
23	ILC (7)	10	2	48	IDC (5)	5	1
24	ILC (10)	10		49	ILC (5)	6	1
25	ILC (4) or IDC (4)	6		50	ILC (5)	6	

ILC, invasive lobular carcinoma; IDC, invasive duct carcinoma; MED, medullary carcinoma.

TABLE II. Pairwise Agreement Between Observers (%)*

	2	3	4	5	**6**	**7**	**8**	**9**	**10**
1	52–74	40–66	52–70	46–66	56–88	54–70	64–86	38–72	46–74
2		54–70	48–58	18–30	34–76	34–58	44–58	26–38	26–52
3			38–48	16–34	28–60	24–34	40–60	16–28	24–48
4				52–76	42–82	60–70	62–68	62–72	54–84
5					42–80	56–78	42–60	58–80	56–82
6						38–84	42–84	26–70	48–88
7							58–64	64–76	60–84
8								46–58	46–74
9									60–84

*First value indicates complete agreement, while second value reflects combined complete or partial (at least one component of mixed types) agreement. (Pathologists experienced in breast pathology appear in bold **1,6,7,8,9,10.**)

better than that observed in this study. However, there are a considerable number of tumors that may be differently interpreted by different histopathologists, even if they are experienced. A Danish report on cases analyzed by three expert histopathologists yielded kappa values around 0.3 for both ILC and IDC, and gave an overall kappa value close to 0.7 for interexpert agreement [21]. These values are very similar to ours. These results automatically raise the question of the validity of the implementation of mastectomy purely on the basis of a histological report on the presence of ILC, which seems to be highly dependent on who makes the diagnosis.

This is substantiated by follow-up studies. ILC can be treated with wide local excision and axillary surgery, supplemented with adjuvant radiotherapy, chemotherapy, and/or hormonal manipulation. ILC patients treated by such a conservative surgical approach have been reported to have no survival disadvantage as compared with those with IDC [7,22–26].

CONCLUSIONS

The diagnosis of invasive lobular carcinoma seems poorly reproducible. The decision as to whether mastectomy should be performed should not be made purely on

TABLE III. Types of Diagnosis, Their Frequencies and Kappa Values

	All 10 pathologists			6 "expert" pathologists only		
Types of diagnoses	Number of given diagnosis	Kappa values	*P* values for kappas	Number of given diagnosis	Kappa values	*P* values for kappas
ILC	183	0.31	$P < 0.0001$	92	0.43	$P < 0.0001$
IDC	177	0.17	$P < 0.0001$	125	0.27	$P < 0.0001$
ILC + IDC	47	0.1	$P < 0.0001$	39	0.13	$P < 0.0003$
MED	22	0.56	$P < 0.0001$	9	0.38	$P < 0.0001$
AT MED	4	0.05	$P < 0.025$	4	0.09	$P < 0.02$
IDC + MED	2	0	NS ($P = 0.848$)	0	—	
ILC + MED	2	0	NS ($P = 0.848$)	0	—	
BEN	4	0.16	$P < 0.0001$	0	—	
SCIRRH, UNDIFF	4	0.05	$P < 0.025$	0	—	
MUC	9	0.89	$P < 0.0001$	6	1	$P < 0.0001$
ILC + MUC	1	0	NS ($P = 0.924$)	0	—	
TUB	8	0.18	$P < 0.0001$	6	0.25	$P < 0.0001$
TUB + IDC	13	0.13	$P < 0.0001$	9	0.24	$P < 0.0001$
CRIBR	2	0	NS ($P = 0.848$)	0	—	
METAPL	1	0	NS ($P = 0.924$)	0	—	
IDC + TUB + CRIBR	1	0	NS ($P = 0.924$)	0	—	
ILC + TUB	11	0.1	$P < 0.0001$	6	0.18	$P < 0.0001$
IDC + ILC + TUB	4	−0.01	NS ($P = 0.701$)	4	−0.01	NS ($P = 0.715$)
IDC + CRIBR	3	−0.01	NS ($P = 0.774$)	0	—	
ILC + CRIBR	1	0	NS ($P = 0.924$)	0	—	
TUB + ILC + CRIBR	1	0	NS ($P = 0.924$)	0	—	
Total (overall kappas)	500	0.23	$P < 0.0001$	300	0.65	$P < 0.0001$

AT MED, atypical medullary carcinoma; BEN, benign lesion; CRIBR, invasive cribriform carcinoma; ILC, invasive lobular carcinoma; IDC, invasive duct carcinoma; MED, medullary carcinoma; METAPL, metaplastic carcinoma; MUC, mucinous carcinoma; SCIRRH, scirrhous carcinoma; TUB, tubular carcinoma; UNDIFF, undifferentiated carcinoma. NS, not significant.

the basis of a histological report of the presence of ILC. It should also depend on clinicopathological features such as the extent or the localization of the disease.

ACKNOWLEDGMENTS

The author acknowledges the collaboration of the following colleagues in the assessment of the cases involved in the present study: T. Barna (Semmelweis Hospital, Department of Pathology, Miskolc), G. Gonda (Haynal Imre University of Health Sciences, Institute of Pathology, Budapest), E. Kálmán (University of Medicine at Pécs, Institute of Pathology, Pécs), J. Kulka (Semmelweis University of Medicine, 2nd Institute of Pathology, Budapest), J. Liechtenstein-Zábrák (Pándy Teaching Hospital, Department of Pathology, Gyula), I. Mórocz (Semmelweis Hospital, Department of Pathology, Miskolc), Z. Orosz (National Institute of Oncology, Department of Oncopathology, Budapest), Z. Sápi (St. John's Teaching Hospital, Department of Pathology, Budapest), A. Tószegi (A. Szent-Györgyi, University of Medicine, Institute of Pathology, Szeged).

REFERENCES

1. Simpson JF, Page DL: Prognostic value of histopathology in the breast. Semin Oncol 1992;19:254–262.
2. Ellis IO, Galea M, Broughton N, et al.: Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. Histopathology 1992;20:479–489.
3. Henson DE, Fielding P, Grignon DJ, et al.: College of American Pathologists Conference XXVI on clinical relevance of prognostic markers in solid tumors. Arch Pathol Lab Med 1995;119:1109–1112.
4. Foote FW Jr, Stewart FW: A histologic classification of carcinoma in the breast. Surgery 1946;19:74–99.
5. Page DL, Anderson TJ, Sakamoto G: Infiltrating carcinoma: Major histological types. In Page DL, Anderson TJ (eds): "Diagnostic Histopathology of the Breast." Edinburgh: Churchill-Livingstone, 1987: 193–235.
6. Perez-Mesa CM: Gross and microscopic pathology. In Donegan WL, Spratt JS (eds): "Cancer of the Breast, 3rd Edition." Philadelphia: W.B. Saunders Co., 1988: 206–249.
7. Sastre-Garau X, Jouve M, Asselain B, et al.: Infiltrating lobular carcinoma of the breast. Clinicopathologic analysis of 975 cases with reference to data on conservative therapy and metastatic patterns. Cancer 1996;77:113–120.
8. Fechner RE: Histologic variants of infiltrating lobular carcinoma of the breast. Hum Pathol 1975;6:373–378.
9. Steinbrecher JS, Silverberg SG: Signet-ring cell carcinoma of the breast. The mucinous variant of infiltrating lobular carcinoma? Cancer 1976;37:828–840.
10. Fisher ER, Gregorio RM, Redmond C, Fisher B: Tubulolobular invasive breast cancer: A variant of lobular invasive cancer. Hum Pathol 1977;8:679–683.
11. Martinez V, Azzopardi JG: Invasive lobular carinoma of the breast: Incidence and variants. Histopathology 1979;3:467–488.
12. United Kingdom Coordinating Group for Breast Screening Pathology: "Pathology Reporting on Breast Cancer Screening, 2nd Edition." Sheffield: NHSBSP Publications, 1995.
13. Ashikari R, Huvos AG, Urban JA, Robbins GF: Infiltrating lobular carcinoma of the breast. Cancer 1973;31:110–116.

14. Dixon JM, Anderson TJ, Page DL, et al.: Infiltrating lobular carcinoma of the breast. Histopathology 1982;6:149–161.
15. DiConstanzo D, Rosen PP, Gareen I, et al.: Prognosis in infiltrating lobular carcinoma. An analysis of "classical" and "variant" tumors. Am J Surg Pathol 1990;14:12–23.
16. Pereira H, Pinder SE, Sibbering DM, et al.: Pathological prognostic factors in breast cancer. IV. Should you be a typer or a grader? A comparative study of two histological prognostic features in operable breast carcinoma. Histopathology 1995;27:219–226.
17. Dixon JM, Anderson TJ, Page DL, et al.: Infiltrating lobular carcinoma of the breast: An evaluation of the incidence and consequence of bilateral disease. Br J Surg 1983;70:513–516.
18. Lesser ML, Rosen PP, Kinne DW: Multicentricity and bilaterality in invasive breast carcinoma. Surgery 1982;91:234–240.
19. Fleiss JL: The measurement of interrater agreement. In Fleiss JL (ed): "Statistical Methods for Rates and Proportions, 2nd Edition." New York: John Wiley and Sons, 1981: 212–236.
20. Landis JR, Koch GG: The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
21. Kiaer H, Andersen JA, Rank F, Pedersen BV: Quality control of patho-anatomical diagnosis of carcinoma of the breast. Acta Oncol 1988;27:745–747.
22. Schnitt SJ, Connolly JL, Recht A, et al.: Influence of infiltrating lobular histology on local tumor control in breast cancer patients treated with conservative surgery and radiotherapy. Cancer 1989; 64:448–454.
23. Poen JC, Tran L, Juillard G, et al.: Conservation therapy for invasive lobular carcinoma of the breast. Cancer 1992;69:2789–2795.
24. Silverstein MJ, Lewinsky B, Waisman J, et al.: Infiltrating lobular carcinoma. Is it different from infiltrating duct carcinoma? Cancer 1994;73:1673–1677.
25. White JR, Gustafson GS, Wimbish K, et al.: Conservative surgery and radiation therapy for infiltrating lobular carcinoma of the breast. The role of preoperative mammograms in guiding treatment. Cancer 1994;74:640–647.
26. Warneke J, Berger R, Johnson C, et al.: Lumpectomy and radiation treatment for invasive lobular carcinoma of the breast. Am J Surg 1996;172:496–500.

COMMENTARY

Histologic typing of breast carcinoma is still an art rather than a quantitative science. Levels of agreement among pathologists on a variety of malignant and precursor breast lesions generally have been poor [1–3], but can be improved by priming the reviewing pathologist with illustrated instructions immediately prior to a trial [4]. Unfortunately, this is not possible in general practice. The results of Cserni's study are another indication that a simple, standardized guide for breast carcinoma typing such as the World Health Organization publication needs to be established as a single, agreed-on standard. No one should hold their breath waiting for this to happen. Alternative routes have been explored but not generally adopted. They include morphometry, immunohistochemistry, measurements of proliferation or DNA ploidy. Ultimately, only a complete genotypic or extensive multimodal phenotypic assessment would appear to offer a complete solution to the problem. All of these alternative approaches are laden with high costs. The only workable approach for the present would appear to be the training and discipline of pathologists in the use of simplified, brief criteria for identification of specific histopathologic types. Striving for improvement should continue so that type-dependent differences in prognosis and response to therapy among different centers can be compared. Multiinstitutional clinical trials sould employ central pathological review.

John S. Meyer, MD
Department of Pathology
St. Luke's Hospital
Chesterfield, Missouri 63017

REFERENCES

1. Sloane JP, Ellman R, Anderson TJ, et al: Consistency of histopathological reporting of breast lesions detected by screening: Findings of the U.K. National External Quality Assessment (EQA) Scheme. Eur J Cancer 1994; 30A:1414–1419.
2. Rosai J: Borderline epithelial lesions of the breast. Am J Surg Pathol 1991;15:209–221.
3. Palazzo JP, Hyslop T: Hyperplastic ductal and lobular lesions and carcinomas in situ of the breast: Reproducibility of current diagnostic criteria among community- and academic-based pathologists. Breast J 1998;4:230–237.
4. Schnitt SJ, Connolly JL, Tavassoli FA, et al.: Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. Am J Surg Pathol 1992;16:1133–1143.